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13. ABSTRACT (Maximum 200 Words) The goals of this research are to develop interdisciplinary studies of the etiology, biology and prevention of ovarian cancer. Project I, Ovarian Cancer Consortium has registered 955 participants including 464 high-risk women representing 329 families. The Core Laboratory has collected, processed and banked biospecimens from 496 subjects. Project II, Facilitating Decision Making About Prophylactic Oophorectomy: we accrued 80 participants with a family history of ovarian cancer into the study. At the three-month follow up assessment, 86% of participants (68/80) completed and returned their packets. Seventy-four percent of women (59/80) continued their participation through the 6-month assessment, and 69% (55/80) completed the final questionnaire packed at the 12-month assessment time point. Project III, Phase II Chemoprevention Study of Ovarian Cancer: this placebo-controlled randomized protocol using 4HPR has been written, approved by the Dept. of Defense, the National Cancer Institute Chemoprevention Branch, and the FDA. The Gynecologic Oncology Group has implemented the study throughout the country for interested gynecologic oncologists. Data entry and quality control systems have been established and 14 different case report forms are finalized. Seven women have signed consent forms, 6 were enrolled in the Ovarian Tissue Donation Portion of the study, and one has randomized to treatment and completed her prophylactic oophorectomy in March 2000.				
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PROJECT I

**OVARIAN CANCER CONSORTIUM
FOR RESEARCH AND SURVEILLANCE (OCCRS)**

Project Director	Mary B. Daly, M.D., Ph.D.	Fox Chase Cancer Center
Co-Investigator	Andrew K. Godwin, Ph.D.	Fox Chase Cancer Center
Statistician	Andre Rogatko, Ph.D.	Fox Chase Cancer Center

INTRODUCTION

Ovarian cancer continues to pose a significant threat to mortality in the 23,300 women estimated to develop the disease in the United States in 2002. The search for a clearer understanding of the causes of the disease as well as how to prevent and detect it is underway through research efforts such as the Ovarian Cancer Consortium for Research and Surveillance (OCCRS). The OCCRS, now in operation at Fox Chase Cancer Center for four years has had a steady base of recruitment through established networking procedures. Current enrollment of 955 participants includes 180 ovarian cancer patients and 464 high-risk women, 26 male relatives and 285 proxy representing 329 families from 41 states and Canada. While continuing to enlist new individuals into the OCCRS, staff has focused on the recruitment of extended family members and the procurement of medical records, blood samples and tumor tissue specimens. The relational database system is constantly updated to include incoming information. Laboratory research continues as directed by Dr. Andrew Godwin. Significant progress has been made in the Symptom Checklist Project. We continue to promote ovarian cancer research awareness through various outreach and advocacy activities and are encouraged by the ongoing community support.

BODY

Established procedures for recruitment of participants and collection of data and biospecimens allowed for increased activity in the OCCRS during year four. The following is a description of the research accomplishments associated with each Task as outline in the approved Statement of Work.

Task 1. Development and Implementation of a Recruitment Strategy

Key personnel actively involved are listed in **Appendix A**. The collaborative sites, Reading Medical Center, Wake Forest University Baptist Medical Center, and Cooper Medical Center encountered a variety of logistical issues that curtailed the numbers of women recruited into the study at those sites. Such issues, which should be considered when designing future joint research efforts, included changes in staff committed to the project, and extended length of time required to operationalize recruitment procedures (due to IRB processes and development to population-specific marketing and networking strategies). Also it has been noted that ovarian cancer patients, while often motivated to help research, may be dealing with treatment-related issues that can compromise follow-through with study requirements.

Total Participation from all sites (including FCCC):

To date, 955 participants, including 180 patients and 464 high-risk women, 26 male relatives, and 285 proxy individuals, representing 329 families are enrolled. Of these families, nine are from Reading, 31 from Wake Forest and 17 from Cooper. Two hundred forty-seven (247) families had one case of ovarian cancer, 60 had two cases and 22 had more than two. One hundred ninety-one (191) families had both breast and ovarian cancer, supporting the clustering of these cancers in women with *BRCA1* and *BRCA2* mutations. The median age of OCCRS participants is 48 years, with a range of 16 to 93 years (age and range do not include proxy individuals). Participants live in 41 states and Canada. Overall compliance of recruited individuals was high with 60 individuals who agreed to participate but never returned paperwork.

Task 2. Establishment of a Computerized Data Base

The relational database system continues to maintain all information obtained in this research. Health history, family history, clinical, epidemiologic, socio-demographic, psychosocial and laboratory data are continually added to the system and annual follow-up data is collected from all participants as per standard FRAP protocol. Multigenerational pedigrees are generated for all probands.

Task 3. Development of Informed Consent Practice

Ongoing review for the OCCRS (Fox Chase Cancer Center protocol # 98-820) was performed by the IRB on 8/26/02. Reapproval of the Symptom Checklist substudy was incorporated into the ongoing review for the OCCRS. Informed consent is obtained from all participants as part of recruitment into the study.

Task 4. Establish an Ovarian Cancer Tissue Bank

Biospecimen collection continues via established procedures. As noted earlier it has been a challenge to encourage extended family members to return blood sample kits. To date, the Core laboratory has collected, processed and banked biospecimens (e.g., serum, platelets, DNA, and lymphocytes) from 536 blood samples. Four hundred sixty-seven (467) samples were collected through Fox Chase Cancer Center, 42 through Wake Forest, 10 through Reading and 17 from Cooper.

Additionally, 96 sets of tumor tissue blocks and/or slides have been released to Fox Chase Cancer Center (FCCC) from various pathology departments in hospitals where OCCRS participants had surgery.

Task 5. Development and Implementation of Symptom Checklist

The goal of interviewing 50 newly diagnosed patients has been met with 53 interviews completed, either in person or over the telephone. After obtaining informed consent, the interviews were recorded and transcribed. Preliminary analysis of the data shows that 51 of 53 patients experienced symptoms prior to diagnosis, including pain, bloating, bladder and bowel changes among others. Of note is the finding that all 13 patients in the sample with Stage I disease had symptoms. Development of the checklist tool will be undertaken after the interview analysis is completed. Future plans include a prospective study to validate the symptom checklist.

Task 6. Standardization of Genetic Risk Counseling Protocols

The comprehensive genetic risk counseling protocol developed in the Margaret Dyson Family Risk Assessment Program at FCCC is the model for the programs at the Reading Medical and Cooper Medical Centers. The Wake Forest site collaborates with a certified genetic counselor to provide risk counseling.

Task 7. Develop a Comprehensive Education Program for Providers and Participants

We continue to use a sophisticated compact disc-interactive (CD-i) format for educational purposes, alerting women at risk to the genetic basis, screening and prevention of ovarian cancer. This format is complemented by a personal binder of information provided to each participant, to serve as a reference and enhance the cancer risk counseling process.

All participants in FRAP receive a periodic newsletter, *Prevention Matters*, with an article devoted to ovarian cancer research and education (**See Appendix B**).

The FCCC website, <http://www.fccc.edu> is updated on a regular basis and includes institution-specific information on ovarian cancer treatment and risk assessment. The site links to comprehensive ovarian cancer educational information through the Cancer Information Service.

On an annual basis the project manager participates in a local advocacy walk, the National Ovarian Cancer Coalition's "Walk for the Whisper" to raise awareness. Educational materials are shared with the public regarding screening, prevention and risk assessment for ovarian cancer.

On September 26, 2002 we premiered our Fox Chase Cancer Center Ovarian Cancer Awareness Quilt at a special reception in our Cancer Prevention Pavilion lobby to promote increased understanding of issues related to ovarian cancer. The quilt was the culmination of a two-year effort by patients, family members and staff to craft a unique tribute to persons with ovarian cancer. It will be used for awareness events both at the Center and in the community.

Funding will be sought to develop a more formalized counseling module for women considering prophylactic oophorectomy. Building on focus group information from women who have had surgery we hope to more fully address the needs of women experiencing surgically induced menopause, including the management of menopausal symptoms, cardiovascular health, and osteoporosis, within a comprehensive women's health approach.

KEY RESEARCH ACCOMPLISHMENTS

- Obtained and banked 536 blood samples into the OCCRS during the course of the grant
- Distributed DNA from blood and ovarian tumors to multiple investigators for various studies
- Collected 37 overtly normal ovaries from women undergoing oophorectomies. Two (2) of these individuals had participated in the 4-HPR chemoprevention trial.
- Identified 36 germline mutations in the OCCRS participants

REPORTABLE OUTCOMES

None.

CONCLUSIONS

Recruitment into the OCCRS has been steady, fueled by the growing community interest in ovarian cancer advocacy. Our numbers have not met those originally proposed, due in part to the logistical challenges encountered by our collaborating sites. Each site took at least one year to become fully operational and staff changes posed additional constraints. The compliance rate of those who did participate is high, despite the fact that many ovarian cancer patients experience

recurrent disease and its challenges. The compliance rate of extended family members has been lower than that of the probands.

Now that a sizable resource has been collected we anticipate ongoing analysis of the data to provide important insight into the genetic basis of oncogenesis, epidemiology and symptoms of ovarian cancer.

REFERENCES

None

FINAL REPORT

PROJECT II

**FACILITATING DECISION MAKING ABOUT
PROPHYLACTIC OOPHORECTOMY**

Project Director
Co-Investigator

Dr. Suzanne M. Miller
Dr. Carolyn Y. Fang

Fox Chase Cancer Center
Fox Chase Cancer Center

INTRODUCTION

Project II, *Facilitating Decision-Making about Prophylactic Oophorectomy*, focused on how women with a familial risk of ovarian cancer make decisions regarding their preventative options, specifically prophylactic oophorectomy (surgical removal of healthy ovaries). The primary goal of the study was to explore the psychological factors that influence a woman's decision to undergo or forego the procedure. A secondary goal was to identify whether high monitors (who typically scan for and exaggerate cancer threats) show a different pattern of response than low monitors (who typically distract from and minimize health threats). Data obtained from this study will be used to develop an enhanced counseling intervention to facilitate decision-making and maximize patient adjustment.

BODY

During the initial year of funding, considerable attention was devoted to careful start-up efforts. Modifications to the protocol were implemented in order to ease participant burden and to clarify requirements and directions. In addition, a procedural plan was designed to ensure consistency in dealing with multiple sites. This entailed identifying key personnel, developing a standardized protocol to contact potential participants, and the establishment of a computerized database for all study data. A series of meetings held between staff at FCCC and contacts at collaborating sites enabled us to systematically develop and enact this plan. The study was conducted at Fox Chase Cancer Center, as well as at satellite sites including Cooper Health System and Reading Hospital. Four evaluation time-points included a baseline assessment with 3-, 6-, and 12-month follow-up assessments. Measures included background variables (i.e., demographics, personal health history, medical status), person variables (i.e., attentional style), process variables (i.e., the patient's level of perceived risk, perceived control, distress, values/goals, and self-regulatory coping strategies), and outcome variables (i.e., decision-making regarding prophylactic oophorectomy). Data obtained from this study will be used to develop an enhanced counseling intervention to facilitate decision-making and maximize patient adjustment. The Cognitive-Affective Processing (CAP) intervention will be designed to enable the prophylactic oophorectomy candidate to realistically anticipate scenarios that might develop, thereby providing a more informed basis for making her surgery decision and dealing with its consequences. A pilot study will be designed and conducted to provide a preliminary evaluation of the feasibility and efficacy of the CAP intervention.

During the course of the project, we accrued 80 participants with a family history of ovarian cancer into the study. At the three-month follow-up assessment, 86 percent of participants (68/80) completed and returned their packets. Seventy-four percent of women (59/80) continued their participation through the 6-month assessment, and sixty-nine percent (55/80) completed the final questionnaire packet at the 12-month assessment time point. No adverse events were reported during the course of the study. Findings from the project have been reported at national conferences and published in peer-reviewed journals. Specific findings are reported below.

KEY RESEARCH ACCOMPLISHMENTS

- Implemented study protocol at Fox Chase Cancer Center, Reading Hospital, and Cooper Hospital
- Accrued 80 participants into the research database
- Collected longitudinal data on diverse psychosocial measures, including assessments of perceived ovarian cancer risk, psychological adjustment, and coping strategies
- Completed and published a review and analysis of the literature on decision-making about prophylactic oophorectomy. This review paper, *Decision Making about Prophylactic Oophorectomy among At-Risk Women: Psychological Influences and Implications*, was published in *Gynecologic Oncology* (Miller, Fang, Manne, Engstrom, & Daly, 1999).
- Published a second review paper that integrated the ovarian risk literature within a theoretical framework of health threat and health behaviors. This review (Miller, Fang, Diefenbach, & Bales, 2001) was published as a chapter in *Psychosocial Interventions for Cancer*.
- Published an empirical paper entitled *Anxiety/Uncertainty Reduction as a Motivation for Interest in Prophylactic Oophorectomy in Women with a Family History of Ovarian Cancer* in the *Journal of Women's Health* (Hurley, Miller, et al., 2001). This manuscript investigated the relation of cancer anxiety and other factors to interest in prophylactic oophorectomy in a group of women with varying degrees of familial risk for ovarian cancer.
- Published another empirical paper, *The Influence of Attentional Style and Risk Perceptions on Intentions to Undergo Prophylactic Oophorectomy Among FDRs*, in *Psychology and Health* (Fang, Miller, Daly, & Hurley, 2002). This paper illustrates the impact of monitoring attentional style and perceived risk on at-risk women's intentions to undergo prophylactic oophorectomy.
- Completed a detailed analysis of the relationship between psychosocial factors and intention to undergo prophylactic oophorectomy in the near future (i.e., next 12 months). Several cognitive beliefs were associated with women's intentions. This analysis is reported in a manuscript under review at *Preventive Medicine* (Fang, Miller, et al., under review).

REPORTABLE OUTCOMES

Demographic Characteristics of Study Participants

Participants were on average 42 years of age ($SD = 10.04$, range = 22 to 71). The majority of participants (65%) had earned a college or post-graduate degree and were married (78%). Most participants (70%) had one first-degree relative with ovarian cancer, twenty-three percent of participants had two relatives with ovarian cancer, and one participant (1%) had 3 relatives with ovarian cancer.

Psychosocial Profile of Study Participants at Baseline (Study Entry)

Participants reported low levels of anxiety ($M = 1.96$, $SD = 2.36$, range = 0 to 12) and depression ($M = 2.72$, $SD = 3.13$, range = 0 to 12). However, the majority of participants (83%) perceived themselves to be at somewhat greater or much greater risk for developing ovarian cancer than other women their age with a family history of ovarian cancer. Approximately 13 percent reported that they were at the same level of risk as a comparable group of women. A minority of women (4%) stated that they felt at somewhat lower risk.

The mean of the perceived benefits scale was 7.41 ($SD = 4.23$), with scores ranging from 0 to 15. The fact that ovarian cancer is difficult to detect in its early stages was viewed by most participants (73%) as being a reason to undergo surgery. In addition, forty-two percent of respondents reported relief from fear as being a benefit of having surgery. Thirty-one percent viewed a reduction of uncertainty in one's life as a potential benefit of prophylactic oophorectomy.

The most significant factor weighing against prophylactic oophorectomy was desiring more children, with 42% of respondents endorsing this as a reason not to have surgery. Forty-one percent indicated that taking hormone replacement therapy after surgery was a factor against having surgery. Twenty-eight percent believed that surgery was risky and twenty-five percent indicated that the potential for surgery to reveal one's risk status to one's insurance carrier and/or employer was a reason not to undergo surgery. Nineteen percent indicated that they did not feel that they were at high enough risk for developing ovarian cancer. Seventeen percent agreed that the cost of the surgery was a barrier to having surgery. Finally, fewer than 11 percent of respondents reported that feeling less feminine after surgery was a factor against undergoing oophorectomy.

Intention to Undergo Prophylactic Oophorectomy

Women's levels of intention to undergo prophylactic oophorectomy were varied, with approximately 66% of respondents reporting that they were "not at all" likely to undergo the surgery in the next 12 months. Sixteen percent reported that they were "a little" likely, 11% "moderately" likely, 3% "very" likely to undergo oophorectomy, and 4% "definitely" intending to have the surgery in the next 12 months.

Univariate analyses were performed using a χ^2 statistic to assess associations between demographic and psychosocial variables and intention to undergo prophylactic oophorectomy. For purposes of performing the univariate analyses, women's intention responses were dichotomized as no intent (i.e., "not at all" likely to undergo surgery) or indicating some level of intent. In univariate analyses, no demographic variables were found to be associated with intention. Levels of anxiety and depression (based on median split) were also not associated with reported intention to have surgery.

However, a number of cognitive beliefs were found to be associated with intention to have surgery. Specifically, participants who agreed that the benefits of surgery included relief from fear of getting cancer and a reduction in uncertainty in one's life were more inclined to have surgery ($ps < .05$). Surprisingly, only one perceived barrier item (desiring more children) was significantly associated with women's surgical intentions.

A hierarchical regression analysis was performed to identify potential associations between sociodemographic and psychosocial factors and women's intention to undergo prophylactic oophorectomy. Results indicated that greater perceived risk of developing ovarian cancer ($\beta = .32$, $t = 2.86$, $p < .01$) and perceived benefits of surgery ($\beta = .38$, $t = 3.35$, $p < .001$)

were positively associated with intention to undergo surgery. Age was also positively associated with intention to have surgery ($\beta = .25$, $t = 2.01$, $p < .05$). However, childbearing was no longer significantly associated with women's reported intentions.

Follow-up Assessments: Data from 3-month follow-up

To date, we have analyzed data from 64 women who have completed the 3-month assessments. To examine women's changes in intention to undergo surgery, we computed a change score by assessing the difference in women's intentions from baseline to 3-months post-baseline (i.e., a positive score represents a shift toward greater intention to have surgery). Regression analyses indicated that a shift toward greater intention to undergo surgery was associated with the use of seeking emotional support as a coping strategy ($\beta = .43$, $t = 2.78$, $p < .01$) and younger age ($\beta = -.32$, $t = -1.91$, $p = .06$), but not associated with subjective or objective risk status, perceived barriers to surgery, or knowledge.

CONFERENCE PRESENTATIONS

This research has resulted in the following conference presentations:

Fang, C.Y. Facilitating decision making about prophylactic oophorectomy. Presented at the New Investigators Workshop held at the 22nd Annual Meeting of the American Society of Preventive Oncology. March, 1998, Bethesda, MD.

Fang, C.Y., Miller, S., Daly, M., Ohls, L., & Hurley, K. Monitoring attentional style and interest in prophylactic oophorectomy. Poster presented at the 23rd Annual Meeting of the American Society of Preventive Oncology. March, 1999, Houston, Texas.

Fang, C.Y., Miller, S.M., Daly, M.B., Ohls, L.M., & Hurley, K. Psychological factors associated with intention to undergo prophylactic oophorectomy. Poster presented at the 20th Annual Convention of the Society of Behavioral Medicine. March, 1999, San Diego, California.

Miller, S.M. Children's Hospital Zurich Colloquium. Invited lecture on: Coping with health threats: Examples from cancer risk and disease. Zurich, Switzerland, March 1999.

Miller, S.M. University of Sacred Heart Colloquium. Invited lecture on: Health psychology. The example of cancer. Tokyo, Japan, May 1999.

Miller, S.M. University of Tokyo Academic Psychology Meeting Colloquium. Invited lecture on: Implications of cognitive styles for coping with health threats. Tokyo, Japan, May 1999.

Miller, S.M. Mie University Faculty of Medicine Colloquium. Invited lecture on: Application of monitoring blunting styles of coping to cancer research. Mie, Japan, May 1999.

Miller, S.M. Hokkaido Health Sciences University Colloquium. Invited lecture on: Monitoring vs. blunting styles of coping with cancer risk. Hokkaido, Japan, May 1999.

Miller, S.M. Aichi Cancer Center Research Institute. Invited lecture on: Psychological factors in cancer prevention and control. Nagoya, Japan, May 1999.

Miller, S.M. Conference on Societal Structures and Effective Health Behavior in the Elderly. Invited speaker on cancer: Demographic and cognitive-coping risk factors. (sponsored by NIH Pennsylvania State University). College Park, PA, October 1999.

Miller, S.M. National Cancer Institute Fellowship Colloquium Series. Speaker on: Behavioral signatures in cancer prevention and control. Washington, D.C., May, 2000.

Miller, S.M. Ovarian Cancer Investigators' Forum Meeting (Sponsored by the Department of Defense). Speaker on: Ovarian cancer prevention program. Herndon, VA, November, 2000.

Fang, C.Y., Miller, S. M., Longacre, M., Hurley, K., & Daly, M.B. Decision making about prophylactic oophorectomy. Poster presented at the 25th Annual Meeting of the American Society of Preventive Oncology. March, 2001, New York, New York.

Miller, S.M. Annual Meeting of the Society of Behavioral Medicine. Paper on: Monitoring coping style in cancer risk: Cognitive and social determinants of adjustment and adherence. Part of Symposium of Building Bridges from Cognitive-Social Theory to Tailored Health Communications. Seattle, WA, March, 2001.

Fang, C.Y., & Miller, S.M. Paper on: Decision making and prophylactic oophorectomy. Part of the Symposium on Decision Making and Genetics. Presented at the Conference on Enhancing Outcomes in Women's Health: Translating Psychosocial and Behavioral Research into Primary Care, Community Interventions and Health Policy. Washington, D.C., February, 2002.

Fang, C.Y., Miller, S.M., Malick, J., & Daly, M.B. Coping predicts changes in intention to undergo prophylactic surgery. Poster presented at the 23rd Annual Meeting of the Society of Behavioral Medicine. April, 2002, Washington, DC.

CONCLUSION

This research will fill a void in the ovarian cancer risk literature. Women at increased risk of ovarian cancer face a difficult decision regarding preventative surgery, and few resources are available to help them with their decision. Hence, it is important to explore factors associated with decision-making and to use the information to develop effective counseling interventions. Through more systematic investigation of these factors, we have been able to develop a profile of the psychosocial factors that influence decision making, which can be used in the design of an enhanced counseling intervention to facilitate informed decision making about prophylactic oophorectomy. A pilot study is being designed to investigate the effectiveness of such a counseling intervention.

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Miller, S. M., Fang, C. Y., Manne, S. L., Engstrom, P. F., & Daly, M. B. Decision making about prophylactic oophorectomy among at-risk women: Psychological influences and implications. *Gynecologic Oncology*, 75, 406-412, 1999.

Hurley, K.E., Miller, S.M., Costalas, J.W., & Daly, M.B. Anxiety/uncertainty reduction as a motivation for interest in prophylactic oophorectomy in women with a family history of ovarian cancer. *Journal of Women's Health and Gender-Based Medicine*, 10, 189-199, 2001.

Miller, S.M., Fang, C.Y., Diefenbach, M.A., & Bales, C.B. Tailoring psychosocial interventions to the individual's health information processing style: The influence of monitoring versus blunting in cancer risk and disease. In A. Baum & B. Andersen (Eds.), *Psychosocial interventions for cancer* (pp. 343-362). Washington, D.C.: American Psychological Association, 2001.

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Fang, C.Y., Miller, S.M., Babb, J., Malick, J., Engstrom, P.F., & Daly, M.B. Psychosocial correlates of intention to undergo prophylactic oophorectomy among women with a family history of ovarian cancer. Submitted, *Preventive Medicine*.

FINAL REPORT

PROJECT III

**PHASE II CHEMOPREVENTION STUDY
OF OVARIAN CANCER**

Project Director Robert F. Ozols, M.D., PH.D. Fox Chase Cancer Center

INTRODUCTION

Fenretinide, a retinamide derivative of vitamin A, is a promising chemopreventive agent, which induces apoptosis and decreases cell proliferation. It has an inhibitory effect on the growth of ovarian cancer cells and surface epithelial cells of the ovary. This research study tests the hypothesis that treatment of high-risk individuals with fenretinide will change the histologic features associated with a preneoplastic phenotype in ovaries as well as alter putative biomarkers of preneoplasia. To test our hypothesis we are conducting a Phase II clinical trial of fenretinide versus a placebo in women with high risk of developing ovarian cancer and a desire to undergo oophorectomy for prophylaxis. At the completion of the treatment phase of the clinical trial, all patients will undergo oophorectomy, and the histologic characteristics of the ovaries from the two groups of patients will be compared as well as markers of cell proliferation and apoptosis. In addition, these results will be compared to ovaries removed from untreated individuals at no increased risk for ovarian cancer. This study will establish baseline values of SEBs in high-risk and normal-risk populations as well as evaluate the specific effect of fenretinide treatment on cell proliferation and apoptosis in precursor lesions of an ovarian cancer-prone population.

BODY

A total of 71 participants (including a 10% "drop-out" rate) will be randomized to allow 32 evaluable participants per arm. Eligible to participate are women greater than 18 years of age who have decided to undergo a prophylactic oophorectomy due to increased risk for ovarian cancer defined by: 1) evidence of a genetic defect in BRCA1 or BRCA2, or 2) one or more first-degree relatives diagnosed with ovarian cancer prior to the age of 50 years, or 3) other family history contributing to risk: one first-degree relative diagnosed with ovarian cancer at any age and at least one other first- or second-degree relative diagnosed with ovarian cancer at any age.

Participants are randomized to take daily oral doses of either 400 mg 4-HPR or placebo for 4-6 months with monthly 3-day drug holidays. Following this treatment period, the participant undergoes the planned prophylactic oophorectomy 7-10 days after the first day of her menstrual cycle. The primary objectives are to assess the effect of 4-HPR on ovarian histology; and the effect of 4-HPR on potential surrogate endpoint biomarkers (SEBs): apoptosis (TUNEL and immunohistochemistry of single-stranded DNA), apoptosis (regulation (bcl-2 and Bax expression), and one marker of proliferation (MIB-1 protein level). Additional control ovarian tissue will be obtained from: 1) high-risk individuals who are eligible for the trial but uncomfortable waiting 4-6 months for their oophorectomy, and 2) normal, low-risk individuals. These banked tissue samples will assist in evaluating the variability between individuals over time and the significance of SEBs for ovarian cancer. The total duration of the study is three years.

In May 1998, the Department of Defense notified the FCCC of its recommendation to fund our clinical prevention trial "Evaluation of Fenretinide as a Chemopreventive Agent for Ovarian Cancer." The study was submitted to the FCCC Research Review Committee (RRC) in June 1998. This committee reviews proposed clinical studies from the perspective of scientific rationale, study design, feasibility and conduct, patient registration and data management, statistical appropriateness and institutional priority. Additional information and revisions were

requested by the RRC. Following institution of these changes, the study was approved by the RRC and submitted to the Institutional Review Board (IRB).

In August 1998, this IRB-approved clinical trial was reviewed by the Surgeon General's Human Subjects Research Review Board (HSRRB). Additional clarifications were requested and instituted. Approval was granted.

In February 1999, this study underwent review by the National Cancer Institute, Chemoprevention Branch (NCI, CB). The NCI, CB is very supportive of this study and is providing fenretinide as well as placebo. The NCI has certain responsibilities as Sponsor for the Investigational New Drug application (IND) of fenretinide. In order for the NCI, CB to fulfill its responsibilities, the protocol, associated case report forms, and consent were revised for submission to the Federal Drug Administration (FDA) as part of the fenretinide IND application.

In June 1999, this study underwent review and approval by the FDA as part of the fenretinide IND application. In late June 1999, FCCC received fenretinide and placebo from the NCI.

The research protocol review and approval process was complicated and lengthy. As summarized in Table 1, 31 women have been recruited to the study. To date, 4 women have been evaluable per the protocol. Three individuals were enrolled to the ovarian tissue donation portion of the study and have already donated ovarian tissue at the time of their surgery. One woman was randomized to fenretinide or placebo for four months prior to her prophylactic oophorectomy, which was performed in March of 2000.

Recruitment through the family risk assessment program at FCCC continues. Genetic counselors at academic institutions in Pennsylvania have been contacted and given study information to provide to eligible women they may be counseling.

The Gynecologic Oncology Group has implemented this important study through their cooperative group mechanism. This will not only assist in accrual of this limited population but will make this scientifically interesting study available to high-risk women around the country.

KEY ANTICIPATED RESEARCH ACCOMPLISHMENTS

Anticipated key research accomplishments emanating from this research include the following:

- Success in altering the SEBs in this clinical trial format would justify prolonged treatment with fenretinide and provide an alternative to oophorectomy for prophylaxis in women at high risk for ovarian cancer.
- Tissues obtained during this research will be a resource for further studies of molecular carcinogenesis in ovarian cancer. This effort may lead to the identification of specific novel targets for therapy and prevention in patients with hereditary ovarian cancer and the more common sporadic epithelial ovarian cancer.

REPORTABLE OUTCOMES

The research protocol review and approval process was complicated and lengthy. Thus, no individuals have been enrolled to date. However, during this process, data collection and management systems were created in preparation for study activation.

1. Data Entry, Management and Quality Control

The large volume of information to be generated in this project requires the implementation of computer-based tools for the management and coordination of data. The Population Informatics Facility (PIF) is responsible for all database and statistical programming aspects of this study. The purpose of the PIF is to provide Informatics expertise to facilitate the research conducted by investigators at FCCC. PIF personnel designed and developed the appropriate database, created the data entry interface, trained the technicians in its use, and provided regular feedback on data quality.

At recruitment, each subject will be given a unique identification number. Baseline information on health, family and dietary history, along with pretreatment laboratory and clinical test results will be entered onto prepared hardcopy (paper) data collection instruments by a study representative. Upon completion, these forms will be sent to the FCCC Chemoprevention Protocol Office (CPO) where the data will be entered via terminals into the database using the electronic data system created by PIF programmers.

At each subsequent follow-up contact, a study representative will complete hardcopy questionnaires containing information on study subject compliance with pill consumption, toxicity symptoms, results of routine blood sample analyses, and clinical observations made by the attending physician. Similarly, the study representative will place results from all laboratory procedures on hardcopy data collection instruments. These forms will be sent to the Protocol Coordinator for data entry. All laboratory records will include the unique identifier and date of collection of the biologic sample.

The information system for this project was built on the system that has been developed by PIF to support the Chemoprevention Clinical Trials at FCCC. As of May 1, 1999, the Chemoprevention Clinical Trials database stores information on 1,526 study subjects from seven chemoprevention trials at FCCC. This DBMS maintains all of the data collected in these studies and is designed to facilitate many aspects of data collection and patient tracking. Based upon the data entered into the database, this software system is capable of performing such tasks as the determination of study eligibility, automated subject randomization and the generation of mailed reminder letters. Most, if not all, of these capabilities have been incorporated into the systems developed for this project.

The existing database management system uses the relational database product ORACLE as the primary software platform for data entry and validation, storage, retrieval, modification, and security. This software system runs on a UNIX-based distributed computing system. These computers are maintained by the Research Computer Services facility at the Fox Chase Cancer Center. This distributed computing system is an integral part of a Local Area Network (LAN) which provides connections to a Digital VAX computer, IBM compatible PC's, Macintoshes,

printers, plotters, and the Internet. The software developed to meet the needs of this study will also use these computing facilities.

On-screen data entry forms, designed to resemble the data collection instruments, were created using the ORACLE Forms V6.0 software. Data validation will occur both during and after data entry. Range, validity and logical consistency checks will be conducted during the data entry process to ensure data quality. Reports generated from the entered data will be compared to the original data collection instruments to further ensure the accuracy of the data stored on magnetic media. Edits will be conducted using the query-by-form capability of ORACLE. This system of data entry and corrections will allow the data analyst to have access to the most up-to-date and accurate data at any given time. Daily backups of the database will be conducted to protect against accidental corruption or deletion of the data. Statistical computing will be performed using a variety of statistical packages including SAS, BMDP, IMSL, Splus and other custom written programs.

In order to preserve privacy and confidentiality, a series of security measures will be undertaken. Only the person-specific identifier, and date of collection when appropriate, will be stored with study results. Lists of Ids matched with names and addresses will be stored by the investigators in locked filing cabinets. Further, through the use of the security measures available within the operating system (UNIX) and the relational database management software (ORACLE), restrictions will be applied to each user commensurate with their needs to access the data. All new personnel with any access to the data will be trained in the ethics of electronic data access.

2. Case Reports Forms

Data from these studies will be kept in a database consisting of 14 data "tables": (1) Initial Contact/On-study; (2) Eligibility Checklist; (3) Health History Data; (4) Baseline Epidemiologic Data (e.g., smoking and alcohol intake, reproductive history, weight, etc.); (5) Concomitant Medications; (6) Diet Data; (7) Pretreatment signs and Symptoms; (8) Physical Examination; (9) Study Drug Administration; (10) Compliance Measures; (11) Toxicities; (12) Routine Laboratory Studies (e.g., CBC, electrolytes, liver function tests, etc.); (13) Research studies (Mib-1, apoptosis markers, etc.); and (14) Off-study. Some of these tables will have one record per subjects (e.g., Health History Data) while other may have multiple records per subject (e.g., Toxicities), each identified by the individual-specific identification number and date of collection. All tables can be linked by their unique individual identification number (and date of collection, when appropriate).

3. Ovarian Tissue Analysis (Andres Klein-Szanto, M.D., Ph.D.)

Previous research done in our Institution using ovarian tissues from individuals with an inherited predisposition for ovarian cancer indicated that preinvasive lesions probably precede the development of ovarian cancer (1). The histological features of the ovaries from a number of such individuals were compared to ovaries from individuals at no increased risk for ovarian cancer. This study revealed two important findings. First, examination of the ovaries from twenty high-risk individuals revealed two unanticipated near-microscopic malignant common epithelial tumors. The second finding in this early study relates to the histological features of the ovaries in which cancer is likely to develop. These structural features of ovarian surface epithelium (OSE)

lesions are: surface papillae, invaginations, inclusion cysts, pseudostratification or hyperplasia and stromal activity or nodularity. The cancer-prone ovaries contained a range of histological features not usually seen in such magnitude, combination and complexity in control ovaries. A significant number of cases (70% of high-risk ovaries versus 20% of the control group of ovaries) presented multifocal surface papillomatosis ranging from a few foci to markedly extensive. These projections were usually short and stubby, with a fibrous core covered by cuboidal or pseudostratified epithelium. The invaginations were often very deep into the cortex, sometimes with bifurcations or branching. Similar but fewer and less deep invaginations were also observed in 11 of 20 control ovaries.

Another frequent finding in the cancer-prone ovaries was the presence of cortical superficial "inclusion" cysts in 70% of high-risk cases versus 25% of controls. They were of variable size and shape, usually lined by a pseudostratified epithelium of "serous" or tubal type and usually devoid of any contents within the space. In some cases, groups of the cysts of varying complexity occurred creating the appearance of microscopic cystadenomas or adenofibromas.

Occasional mitoses and apoptotic cells were observed in the surface epithelium of cancer-prone ovaries associated with an increase in height and pseudostratification of the tall columnar cells.

In addition to the OSE lesions, the stroma of these organs also appeared to be uncharacteristically active or hyperplastic.

Several later publications published in the last two years have revisited this topic and have reached similar conclusions (2-5). Werness et al (2) found that cancer prone ovaries had significantly more cysts, cortical nodularity and OSE cellular atypia than control ovaries. Casey et al (3) found more surface papillae in ovaries from BRCA1 and BRCA2 patients and Sherman et al (4) and Deligdisch et al (5) concluded that epithelial hyperplasia and atypia are more frequent in susceptible populations than in control patients. Conversely a couple of publications found no significant differences in lesion incidence between ovaries from cancer prone patients and control ovaries (6-7).

During the course of this project we have analyzed a new set of tissues derived from patients with either BRCA1 or BRCA2 mutations (n=29). We compared the OSE lesions in these tissues with those from a control age-matched population (n=27) that underwent oophorectomy for unrelated disease (leiomyomata, cervical cancer and intestinal disease). The cancer prone patients were from the surgery-only arm of our study and did not receive any chemopreventive treatment. The controls were from our archival surgical pathology collection. The tissues were examined separately by two pathologists in a blind fashion. Both invaginations and inclusion cysts were seen more frequently in the high risk population than in the control tissues ($p < 0.001$). The incidence of the other OSE lesions were not found to be statistically different in these two groups.

We investigated the proliferative characteristics of the surface epithelium of these samples Using the proliferative marker Mib-1 we found that the Mib-1 index (percent of positively stained cells or labeling index, LI) of the apparently normal surface epithelium was very low and not significantly different in the two groups. (LI range 0 to 1). Although some differences in LI were found in cysts, invaginations, and papillae, these were not statistically significant. In a few cases

the from cancer prone subjects papillae and cysts had a LI as high as 9%, nevertheless no statistically differences were noted when compared with the control cases.

In conclusion, our new study did not find significant proliferative changes in lesions from ovaries derived from patients at high risk but confirmed previously published results from our own Institution and others indicating that some of these OSE lesions are seen more frequently in ovaries from cancer-prone individuals.

4. Publications/Presentations

Paul F. Engstrom, M.D. presented an overview of this study at the European School of Oncology meeting, September 12-14, 2001, Moscow, Russian Federation.

CONCLUSIONS

The accrual to this study has been unacceptably slow. Two women consented in 1999, five in 2000. There was no accrual in 2001. Of the 7 participants accrued, 6 were tissue donation only; one woman took the drug (fenretinide or placebo). There were no reportable SAEs for the trial. No one is currently enrolled in the study.

In October 2001, the Cooperative Group version of the protocol GOG-0190 will be reviewed by the Fox Chase Cancer Center Institutional Review Board. In the new study design, there is no "tissue only" option; women will consent to be randomized to either immediate prophylactic oophorectomy or to drug for four months followed by prophylactic oophorectomy. We plan to support the tissue analysis portion of the trial on the Ovarian SPORE grant; the Gynecological Oncology Group will be responsible for monitoring accrual, interim reports and analysis of the results of this protocol.

There was no new activity on Project III in 2002.

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FINAL REPORT

LABORATORY CORE

Core Director

Andrew K. Godwin, Ph.D.

Fox Chase Cancer Center

INTRODUCTION:

The molecular genetic events involved in the development of ovarian cancer are poorly understood. Ovarian cancer is the number one gynecologic killer in the United States with over 25,000 diagnosed cases and 14,500 deaths in 1999. A major reason for the high morbidity and mortality associated with ovarian cancer relates to the patterns of dissemination and the absence of signs or symptoms associated with early stage disease. Consequently, most patients are diagnosed with advanced stage (International Federation of Gynecology and Obstetrics [FIGO] III-IV) disease; five-year survival rates for this group of patients are only 20-30%. In contrast, five-year survival rates for patients with limited-stage disease (FIGO I-II) are 70-90%. Thus, understanding the etiology of ovarian cancer remains an important challenge in molecular genetic research. Ultimately, this knowledge may enable the development of better approaches for earlier diagnosis, allowing current therapeutic strategies to be more effective. To support these kinds of studies large numbers of biosamples from well-staged and managed cancer patients and controls is needed. Therefore, the laboratory core was created to collect normal and tumor ovarian tissue as well as blood samples that can be made available for a variety of researcher projects.

BACKGROUND:

The Laboratory Core of the Ovarian Cancer Prevention Program of Fox Chase Cancer Center funded by the Department of Defense, is responsible for the collection, storage, and distribution of biosamples collected as a result of the "Ovarian Cancer Consortium for Research and Surveillance (OCCRS)" and the "Evaluation of Fenretinide as a Chemopreventive Agent for Ovarian Cancer".

BODY:

The goals of this laboratory core have been met (i.e., collect and distribute biosamples), however the number of participants recruited into the Ovarian Cancer Consortium for Research and Surveillance (OCCRS) and the fenretinide chemoprevention study were less than predicted. Nevertheless, the number of blood samples obtained from OCCRS participants increased steadily over the course of the grant.

SPECIFIC AIMS (PREVIOUSLY PROPOSED):

Specific Aim 1: Collection and banking of blood samples from women with ovarian cancer, and their first- and second-degree relatives as part of the "Ovarian Cancer Consortium for Research and Prevention".

Results:

Six hundred and eighty-seven (687) participants, including 234 ovarian cancer patients and representing 320 families are enrolled. Two hundred thirty-one (231) families had one case of ovarian cancer, 52 had two cases and 21 had more than two. One hundred seventy-four (174) families had both breast and ovarian cancer, supporting the clustering of these cancers in women with BRCA1 and BRCA2 mutations. The median age of OCCRS participants is 48 years, with a

range of 16 to 93 years. The geographic base of recruitment has increased significantly due to networking with national advocacy organizations such that women in 42 states and Canada are enrolled. In support of the OCCRS (**Project 1; "Ovarian Cancer Consortium for Research and Surveillance"**), the Core laboratory has collected, processed and banked biospecimens (e.g., serum, platelets, DNA, and lymphocytes) from 469 blood samples.

- 1) 469 blood samples have been collected through the Ovarian Cancer Consortium for Research and Surveillance.
- 2) 469 blood samples have been process and the serum, platelets, and lymphocytes were banked and genomic DNA isolated from "buffy coats".
- 3) 545 samples (either DNA or whole blood) recruited through the Ovarian Cancer Clinical Network were distributed to program project participants and FCCC Investigators (275 whole blood samples to Dr. R. Raftogianis, FCCC, 150 DNA's to A. Yeung, FCCC, and 120 DNA's to T. Hamilton, FCCC).

Change in personnel/facilities:

To improve and standardize the collection and processing of blood samples, FCCC established under the direction of Dr. Godwin, the Biosample Repository in November of 1999. This new laboratory is located on the second floor of the Cancer Prevention Pavilion and occupies ~900 square feet of space with the appropriate equipment including liquid nitrogen freezer space to bank ~72,000 cryovials.

Ms. J. Dangel, Chief Technician in the Department of Pathology at the Fox Chase Cancer Center, was appointed manager of the Biosample Repository in 1999 and was responsible for CAP accreditation and CLIA approval. Her roll is to process blood samples submitted to the Repository (through the Ovarian Cancer Consortium for Research and Surveillance). Samples to be tested for mutations in *BRCA1* and/or *BRCA2* are submitted to Clinical Molecular Genetic Laboratory at FCCC. Ms. Dangel is also responsible for entering collection data regarding the biospecimens into the centralized computer database.

Specific Aim 2: Collection and distribution of archival ovarian tumor and prophylactic oophorectomy specimens as part of the "Ovarian Cancer Consortium for Research and Prevention".

Results:

- 1) 34 ovarian tumor specimens were collected following surgery at Fox Chase/American Oncologic Hospital and were flash-frozen and stored in liquid nitrogen.
- 2) 96 fresh-frozen ovarian tumors were given to Dr. J. Testa (FCCC) to evaluate the levels of activity of AKT, AKT2, and AKT3.
- 3) 22 DNA's from ovarian tumor showing LOH on 6q (and matching constitutive DNA-see above) were given to Dr. T. Hamilton to support mutational analysis of *LOT-1*.

4) During the course of the grant we collected ovarian tissue from 37 women, ages ranging from 34 to 79 years of age. The samples have been collected from 27 different hospitals throughout the United States. Tissue collected at sites other than Fox Chase are arranged through the attending pathologist at the off campus site and a kit is mailed to either the surgeon or the pathologist.

- a) Eight (8) of the women were determined to have a *BRCA1* mutation.
- b) Three (3) of the women were determined to have a *BRCA2* mutation.
- c) Three (3) of the women are from families with a mutation in *BRCA1* (2) or *BRCA2* (1). However, the individuals have declined clinical genetic testing. We are currently screening DNA samples isolated from ovarian tissues to determine if the women from these *BRCA1* or *BRCA2* mutation families are carriers.
- d) Thirteen (13) are from families with a history of breast/ovarian cancer which have not yet been tested for *BRCA1* or *BRCA2* mutations
- e) Ten (10) are from families with no family history of breast or ovarian cancer, which have tested negative for a *BRCA1* or a *BRCA2* mutation.
- f) Tissue sections of all of the ovaries were given to Dr. A. Klein-Szanto for immunohistochemical staining of various markers and pathological review.

5) Primary cell lines were generated from the ovaries of the *BRCA1* and *BRCA2* mutation carriers as well as control individuals.

a. These cell cultures are being used in a collaborative study with Dr. A. Knudson (Senior Member, FCCC) entitled "Evaluation of *in vivo* and *in vitro* pharmacology and toxicology of preventative agents using human mutant cells from dominantly heritable cancers" to study the changes in gene expression following treatment with a variety of chemoprevention agents in culture.

b. Three (3) primary human ovarian surface epithelial (HOSE) cell cultures and 3 mortal, SV40 expression and 3 matching immortal SV40 expressing HOSE cell lines were given to Drs. P. Engstrom (P.I.) and C. Patriotis (Associate Member, FCCC) for evaluation of changes in gene expression patterns following 4-HPR treatment.

Specific Aim 3: Collection and processing of prophylactic oophorectomies from women participating in the chemoprevention trial as part of the "Evaluation of Fenretinide as a Chemopreventive Agent for Ovarian Cancer".

Results:

In order to find women eligible for the 4-HPR trial, we have tested a number of participants of the FRAP for mutations in *BRCA1* and/or *BRCA2* as outlined below. Genetic testing is not funded through this application, but is necessary to increase the pool of women likely to elect to undergo prophylactic surgery.

1) DNA samples from a total of 480 individuals (obtained through the OCCRS or high-risk clinics at FCCC) were tested (either partially or completely) for mutations in *BRCA1* and/or *BRCA2* during the last year

a) 480 DNA samples were tested for three Ashkenazi Jewish founder mutations (i.e., 185delAG and 5382insC for *BRCA1*, and 6174delT for *BRCA2*) using a Heteroduplex Mobility Assay (HMA).

b) 158 samples were tested for mutation in 23 exons and a limited number of adjacent intronic base pairs of *BRCA1* using an enzymatic mutation detection (EMD) assay and direct sequencing.

c) 45 samples were tested for mutations in 26 exons and a limited number of adjacent intronic base pairs of *BRCA2* by direct sequencing.

2) Genetic test results were given to Dr. M. Daly (Senior Member, Director of the Family Risk Assessment Program) and *BRCA1* and *BRCA2* mutation carriers were approached for participation in the 4-HPR chemoprevention trial.

3) Ovarian tissue specimens were collected from 2 women who elected to undergo prophylactic oophorectomies at Fox Chase

a) The two women that participated on the 4-HPR trial reported a family positive family history of breast and ovarian cancer, but had not been previously tested for a *BRCA1* or a *BRCA2* mutation.

b) Tissue sections of all of the ovaries were given to Dr. A. Klein-Szanto for immunohistochemical staining of various markers and pathological review.

c) DNA was isolated from the ovarian tissue and is being evaluated in the Clinical Molecular Genetics Laboratory for mutations in either *BRCA1* or *BRCA2*.

4) A limited number of DOD participants have been tested for germline mutations in *BRCA1* and/or *BRCA2*. Four (4) *BRCA1* have been detected in 33 of the participants which were randomly selected and twenty-three (23) mutations in *BRCA1* and/or *BRCA2* were uncovered in women of Ashkenazi Jewish heritage. Further studies by our group are scheduled to determine the prevalence of germline *BRCA1* and *BRCA2* mutations in population-based samples of ovarian cancer cases in the U.S. and Canada (as indicated below).

KEY RESEARCH ACCOMPLISHMENTS:

- ◆ Obtained and banked 469 blood samples into the OCCRS during the course of the grant.
- ◆ Distributed DNA from blood and ovarian tumors to multiple investigators for various studies (as outlined below).
- ◆ Collected 37 overtly normal ovaries from women undergoing oophorectomies. Two of these individuals had participated on the 4-HPR chemoprevention trial.
- ◆ Identified 36 germline mutations in the OCCRS participants.

REPORTABLE OUTCOMES:

- ◆ In total we have collected 64 ovaries (27 women donated both their left and right ovaries, 6 donated only the left ovary, and 4 donated only the right ovary). We have successfully initiated primary HOSE cell cultures from many of these tissues.

CONCLUSIONS:

Collection of ovarian cancer tissue (tumor and normal) and blood biospecimens is ongoing, due in part to the high compliance rate of the participants. Laboratory research is underway using DNA from these samples to:

- 1) Determine the prevalence of germline *BRCA1* and *BRCA2* mutations in population-based samples of ovarian cancer cases in the U.S. and Canada.
- 2) Estimate the penetrance of germline *BRCA1* and *BRCA2* mutations and compare these estimates across:
 - a) genes (*BRCA1* vs. *BRCA2*)
 - b) mutation type (Ashkenazi Jewish founder mutations vs. all others)
 - c) method of family ascertainment
- 3) Identify novel genetic polymorphisms in the human arylsulfatase gene from 150 samples; a SNP in the 3'-flanking region has been identified.
- 4) Identify common alleles in the human UDP-glucuronosyltransferase gene, *UGT1A6*. Thus far four common alleles have been identified and will be further characterized for functional significance with funding from a DOD Breast Award.
- 5) Identify novel genetic polymorphisms in the human sulfotransferase gene, *SULT2B1*; this project is in the beginning stages.
- 6) Determine if *LOT-1* on chromosome 6q is maternally imprinted and if loss of the paternal allele is involved in ovarian carcinogenesis.
- 7) Determine if germline mutations (and/or polymorphisms) in various repair genes are present at a higher frequency in 100 ovarian cancer patients as compared to 100 age-matched controls.

Overall, we have established a valuable resources through the Core laboratory that will continue to provide important insights with regard to molecular genetic mechanisms associated with ovarian epithelial oncogenesis as well as a better understanding of the biological and biochemical pathways which are altered in response to chemopreventive treatments. The samples will continue to be made available through the Biosample Repository at FCCC and through support of the NIH.

REFERENCES

None.

FINAL REPORT

DATA MANAGEMENT CORE

Core Director

Eric A. Ross, Ph.D.

Fox Chase Cancer Center

INTRODUCTION:

The varied populations studied in this Ovarian Cancer Prevention Program and the complexity of the designs required the development and support of program-specific computer based tools to provide critical project management and coordination, and for the collection, validation, storage, retrieval and analysis of data. The projects contained in this program project grant (PPG) include: the Ovarian Cancer Consortium for Research and Surveillance, the Facilitating Decision-Making About Prophylactic Oophorectomy, and the Phase II Chemoprevention Study of Ovarian Cancer studies.

The specific aims of the Data Management Core (Core) were to:

1. Provide computer-based tools that facilitate the entry, storage, manipulation and retrieval of the large quantities of data generated.
2. Ensure the accuracy of the data maintained in the database by developing human and software based data consistency and quality control systems.
3. Provide high-quality data entry services.
4. Organize and maintain the database to maximize accessibility, while maintaining strict confidentiality.
5. Provide statistical computing support.

BODY:

Statement of Work:

Months 1-12: (1) Core staff will meet with research staff to refine and finalize the data flow and hardcopy data collection instruments. (2) Data Dictionaries will be developed. (3) Database design will be finalized by the Facility Director and Database Programmers. (4) The database management systems developed for the FRAP/CFRBCS project and the Chemoprevention Clinical trials will be modified to implement the database for this program project. (5) Electronic data entry forms will be designed, and implemented by the Database Programmers. (6) Software for the scheduling of follow-up visits, the distribution of mailed self-report questionnaires, and the generation of contact logs for conducting telephone interviews will be developed. (7) All software will undergo thorough testing.

Months 3-48: (1) Data quality assurance and quality control procedures will be developed and implemented. (2) Research staff will be instructed in data coding procedures. (3) The Data Entry Clerk and laboratory technicians will be trained in the use of the electronic data entry forms. All data delivered to the Core will be efficiently and accurately entered by the Data Entry Clerk into the database. (4) Post-data entry, data validation software will be developed, tested and utilized. All data will be reviewed upon receipt and aberrant values will be corrected. (5) Daily backups of the database will be conducted.

Months 6-48: (1) The Database Programmer will perform all tasks necessary to ensure that the database functions in an efficient manner. The database will be modified by the Database Programmer, as necessary, to ensure that the database software meets the needs of the projects that compose the Program Project. (2) Software for the generation of reports concerning each study's progress will be developed, tested and periodically executed. (3) Software to allow for

the extraction of data for analysis purposes will be developed, tested and utilized upon request. (4) Statistical programming tasks may be conducted by Core staff under the direction of the study statisticians.

The goals of this core have been met.

KEY RESEARCH ACCOMPLISHMENTS:

- Core staff collaborated with project investigators and research staff to refine and finalize the data flow and hardcopy data collection instruments. Core staff developed data dictionaries based on the study requirements and the final data collection instruments.
- Core personnel have designed and developed a comprehensive information management system to meet the specific needs of this PPG. The customized relational database system has been implemented using ORACLE database software. The database and management structure facilitated efficient data capture and manipulation, as well as the controlled exchange of information across the several projects. All software underwent thorough testing before release to the user community.
- Client-server and web-enabled electronic data entry/retrieval and report generation software have been developed using the Oracle Developer/2000 suite of products.
- Data quality assurance procedures have been implemented, using software-based data entry checks as well as post-entry manual audits.
- Data entry services were being provided by a Core data entry clerk using the electronic data entry screens developed by Core programmers. Any observed aberrant data values were corrected in the database.
- Software for the scheduling of follow-up visits, and the distribution of mailed self-report questionnaires were developed and deployed.
- Software was developed to generate reports to allow tracking of study accrual and progress of individual study subjects.
- Software was developed for extracting data from the relational database.
- Core personnel supported all aspects of the information management system.
- The database was backed-up to tape on a daily basis. Periodically, a copy of the database backup tape was sent to an off-campus facility for secure storage. Username and password control were used to ensure that investigators and research staff only had access to the information approved for their use. All FCCC computers used for storing the information were protected from inappropriate outside access by the FCCC firewall.
- Core staff performed statistical programming using standard packages (e.g., SAS) under the direction of the study statisticians and investigators.

REPORTABLE OUTCOME:

All data collected in the three research projects as well as data generated by the Laboratory Core are being stored in this information system. The details of the information system developed for this the three research projects are described below.

Project I: The Ovarian Cancer Consortium for Research and Surveillance:

Included in this portion of the PPG information system is health history, clinical, epidemiologic, socio-demographic, psychosocial and laboratory data. In addition, this database contains cancer and vital status data on relatives of individuals recruited into the study. A web-enabled interface to the information system has been developed to maintain the biosample collection, preparation, shipping/receiving and inventory data. The software system coordinates numerous tasks, including the scheduling of follow-up visits, and the distribution of mailed self-report questionnaires. This system is capable of generating multigenerational pedigrees from the union of family histories provided by two or more distinct study subjects in the same family. The family data is easily updated from follow-up information to include deaths or new cancers reported for study subjects, previously listed family members, as well as new births. Currently, data from 670 live participants and 285 proxy questionnaires are stored in this database. The database also contains laboratory inventory and processing information on blood samples collected from 536 registry participants and tissue blocks and/or slides from 96 individuals.

Project II: Facilitating Decision-Making About Prophylactic Oophorectomy:

The database system provides the means for entry, storage and manipulation of all the psychosocial, outcome and study-related data collected in this project. Software has been developed to automatically distribute mailed self-report questionnaires. Information obtained from 80 study subjects have been entered into the information system.

Project III: Phase II Chemoprevention Study of Ovarian Cancer:

The PPG relational database management system also maintains all of the information collected in this phase II clinical study including demographic, health history, pathology, laboratory, study status, adverse reaction and drug compliance data. The software system facilitates many aspects of data collection and patient tracking. This software system uses database information to perform such tasks as: determination of study eligibility, automated subject randomization, and automatic notification of the study biostatistician (via e-mail) of subject randomization. Since initiating the study, seven subjects have been identified as eligible for the protocol. One subject has been randomized.

CONCLUSIONS:

Ovarian cancer is the leading cause of death from a gynecologic malignancy among women in the United States, and ranks second in incidence among gynecologic malignancies. Fox Chase Cancer Center has conducted research in ovarian cancer prevention and control focusing on familial risk of cancer, the behavioral factors influencing the decision to undergo prophylactic oophorectomy, and the effect of chemoprevention agents on precancer structural and molecular markers of carcinogenesis.

This core served as a resource for the PPG as a whole and maintains a valuable source of data for future studies. By centralizing these services into a Data Management Core, we were better able

to manage and coordinate the collection, storage, and distribution of a large amount of highly valuable data. Subject to informed consent, the information contained in the data repository was available to all investigators in the PPG. By providing access to the data to all participants, sharing technical capabilities and ensuring the quality of the data, this core not only facilitated achievement of the aims of the individual projects, but also made possible exploratory analyses beyond the stated aims of the projects.

REFERENCES:

None.

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Fang, C.Y., Miller, S.M., Babb, J., Malick, J., Engstrom, P.F., & Daly, M.B. Psychosocial correlates of intention to undergo prophylactic oophorectomy among women with a family history of ovarian cancer. Submitted, *Preventive Medicine*.

List of Key Personnel paid from project:

None

Salary was not requested for Principal Investigator, Project Directors, Co-Investigators and Statisticians involved in this project.

APPENDICES

- A. Project I, Key Personnel**
- B. Project I, Focus on Ovarian Cancer Research Insert,
*Prevention Matters Newsletter***

APPENDIX A
KEY PERSONNEL

Fox Chase Cancer Center

Principal Investigator: Paul F. Engstrom, M.D.

Project Director: Mary B. Daly, M.D., Ph.D.

Co-Investigator: Andrew Godwin, Ph.D.

Co-Investigator: Betsy Bove, Ph.D.

Statistician: Andre Rogatko, Ph.D.

Project Manager: Carol Cherry, R.N.C., B.S.N., O.C.N.

Genetic Counselor: Josephine Costalas, M.S.

Administrative Assistant: Honey Salador

Data Management: Andrew Balshem

John Malick

Rose Batson

Director of Nursing Research: Andrea Barsevick, R.N., D.N.Sc.

Engstrom, P.F., M.D.

APPENDIX B

Prevention Matters Newsletter



PREVENTION MATTERS

A Newsletter for Family Risk Assessment Program Participants

Winter 2002

Cooperative Family Registry - Genetic Studies in Minority Populations

The Cooperative Family Registry for Breast Cancer Studies (CFRBCS) was established in 1995 as a resource for breast cancer research. Its purpose is to collect information and blood samples from many individuals and some of their family members who have a history of breast cancer and ovarian cancer. Along with Fox Chase Cancer Center (FCCC), several sites in the United States and one each in Canada and Australia participate in the CFRBCS. This registry has succeeded in providing researchers with information on over 5000 families at high risk for breast cancer.

The Institute of Medicine reported in 1999 that funds should be allocated to more fully describe and understand the burden of cancer in ethnic minorities in the United States. Much has been written about racial/ethnic differences in the incidence and mortality of breast cancer, but little is known about the genetic susceptibility among minority populations. Researchers have shown that changes in the *BRCA1* and *BRCA2* genes may

increase an individual's risk of developing certain cancers, and these gene changes can be passed on from parents to children. Research needs to focus on the genetics of minority individuals to learn why there are differences in occurrence, prognosis and survival in this population. FCCC requested and received funds from the National Cancer Institute to support a substudy of the CFRBCS to collect information and blood samples from African American, Hispanic and Asian women with breast cancer and/or a strong family history of breast and/or ovarian cancer. Information pertaining to lifestyle and environmental factors as well as family history and personal medical history will be collected. Cooper Medical Center in Camden, New Jersey will work collaboratively with FCCC to recruit participants for this substudy.

In addition to collecting information and blood samples, genetic testing will be an important component of the study. The following aims have been proposed as areas for research:

- ✦ To estimate how common *BRCA1* and *BRCA2* gene mutations are in each racial/ethnic group;
- ✦ To identify the different types of mutations in these genes;
- ✦ To estimate age-specific risk of breast and other cancers among *BRCA1* and *BRCA2* mutation carriers in each racial/ethnic group, and
- ✦ To search for new genes and gene mutations which may prove to be associated with cancer development.

This study will provide an excellent opportunity to determine the role of genetic predisposition and its interaction with various lifestyle and environmental factors in the development of breast cancer in minority populations. By combining the families recruited through this project with those of the existing CFRBCS, this resource will be the largest family registry database ever assembled.



THE MARGARET DYSON
Family Risk Assessment Program®

Communicating Genetic Test Results to the Family

FRAP's 10th Anniversary Celebration October 22-26, 2001

The Family Risk Assessment Program (FRAP) celebrated its 10th anniversary (see insert) with a week of cancer risk assessment program activities. FCCC staff, patients and visitors were treated to refreshments and gifts, and prizes were given for participating in games pertaining to the risk assessment services available at FCCC and its Network hospitals. The highlight of the week was a special tea held on Wednesday, October 24, 2001. Several FRAP participants shared their stories of how the program had impacted their lives. Dr. Barbara Rimer, Director of the Division of Cancer Control and Population Sciences at the National Cancer Institute was to be the keynote speaker. Due to illness she was unable to attend, but Dr. Paul Engstrom read her speech acknowledging the groundbreaking accomplishments made by the FRAP program in the areas of risk assessment, cancer risk counseling and genetic research.

In addition to the week being a celebration, it also served to raise awareness for the various risk assessment programs that are now available. FRAP's success has served as a model for the development of these programs and has proven that there is truly a need for these services in the community.

The Family Risk Assessment Program at Fox Chase Cancer Center is presently conducting a study to look at how women share their genetic test results with family members. Because of the growing availability of genetic testing, many women at high risk for breast and/or ovarian cancer are taking advantage of these tests. Information about genetics and the risk of disease can be complex and difficult to understand, and talking to a family member about test results can be challenging. Many emotional issues arise for the woman and her family members once this information is known.

This study, funded by the National Cancer Institute, will help us develop tools to assist women in communicating their genetic test results to their family members. We will look at our participants' level of understanding of their own genetic test results and their comfort with sharing these results with their family. We will examine our participants' emotional reaction as genetic information is relayed and

received by family members. We will also survey the informed relatives about their satisfaction with the genetic information received, level of risk comprehension, and intention to seek genetic testing on their own behalf.

To be eligible, a woman must be 18 or over, have a strong family or personal history of breast and/or ovarian cancer and wish to participate in genetic testing. An additional requirement is that the participant must have at least one first-degree relative (parent, sibling or child) with whom she is willing to share her genetic test results.



To learn more about this study, please contact the program coordinator at 215-728-2795 or 1-800-325-4145.

Support Group for Recipients of Genetic Test Results

The Family Risk Assessment Program received funding from the Pennsylvania Department of Health Income Tax Checkoff Program for Breast Cancer Research to pilot test a support group concept for our participants who have received genetic test results. Traditionally, individuals receive intensive preparation to make informed decisions prior to undergoing testing. However, little attention has been given to concerns after genetic test results are received. One of the goals of this pilot project was to determine whether individuals participating in a support group express more long-term satisfaction with their decision to receive test results and undergo genetic counseling.

Four groups consisting of four

weekly sessions were held from January to May 2001. The first hour of each session focused on providing information or education on topics relating to breast and ovarian cancer screening, family issues, nutrition and holistic medicine and stress reduction through yoga. The second hour was reserved for mutual support.

Twenty-six women attended the various sessions, and the majority expressed satisfaction with all aspects of the groups. They also stated that they would be interested in participating in an ongoing group especially if held on a monthly basis. This pilot program helped us to identify trends for the design of a more targeted support group intervention for which we hope to receive funding.

FRAP Celebrates Its 10th Anniversary

1991 - 2001

The Family Risk Assessment Program (FRAP) at Fox Chase Cancer Center (FCCC) began in 1991 by Dr. Mary B. Daly with funding from the Dyson Foundation. It represented a memorial to Margaret Dyson, who died in December 1990 after a brief battle with ovarian cancer. The program's goal has always been to help high-risk women learn about the risk factors and preventive measures associated with breast and ovarian cancer. It was the first comprehensive risk assessment program in the country to provide education, individualized counseling and screening to women at high risk.

Initially, cancer risk education was included in the participant's screening clinic visit. As the program received more exposure, demand for participation grew, and group education sessions were instituted. Individualized genetic counseling was integrated into the program, and genetic testing was added after the breast cancer genes, *BRCA1* and *BRCA2*, were discovered.

The program now includes almost 5,000 participants representing approximately 2,300 families. It has been expanded to several of the Fox Chase Network hospitals as well as Cooper University Hospital in Camden, NJ. Having this large population base of high-risk individuals and family members has enabled us to broaden research in such areas as basic science, nutrition and behavioral medicine. Additionally, collaborations have been formed with other cancer centers and universities throughout the U.S. and internationally. These collaborations have provided many opportunities to

conduct important research that will improve our chance of preventing breast and ovarian cancer.

FRAP has provided a training ground for genetic counseling and public health students, nurses and medical oncology fellows. Educational materials have been developed to provide genetic information to our participants and students. These include an interactive computer module that can be viewed at the individual's own pace, and breast and ovarian cancer risk books that reinforce the information contained in the interactive program. Basic and advanced courses in genetic cancer risk counseling were developed to train nurses and other health care professionals to meet the increasing need for this service.

The success of the program has made possible the creation of several additional risk assessment programs at FCCC – the Prostate Risk Assessment Program, the Gastrointestinal Tumor Risk Assessment Program and the Melanoma Family Risk Assessment Program.

The reason we are able to celebrate FRAP's 10th Anniversary is due to the dedication of its participants. Individuals and families who have unselfishly volunteered to help science and research are directly responsible for the advances made in screening, diagnosis and treatment for cancer. We are all looking forward to many more years of providing this service to high-risk individuals.

10 Years of Risk Assessment Awareness - October 22-26, 2001



Dr. Daly (4th from left) with Family Risk Assessment Program Staff

FRAP FACTS

The risk assessment programs at Fox Chase Cancer Center provide education, individual cancer risk assessment and counseling as well as screening recommendations. These programs are at no charge to individuals who meet the high-risk criteria. Medical evaluation in the individual programs is also available as a billable service. Contact information for each program is listed below.

Margaret Dyson Family Risk Assessment Program

(family history of ovarian or breast cancer):
215-728-2795 or 800-325-4145

Prostate Cancer Risk Assessment Program:

215-728-2406

Gastrointestinal Tumor Risk Assessment Program:

215-728-7041 or 888-369-2427

Melanoma Family Risk Assessment Program:

215-214-1448

FRAP FEEDBACK

"Thanks so much for such a wealth of information. I already left a message to schedule a clinic appointment. Thanks again!"

"You can't imagine what a difference you make. I feel so very, very lucky to have you there."

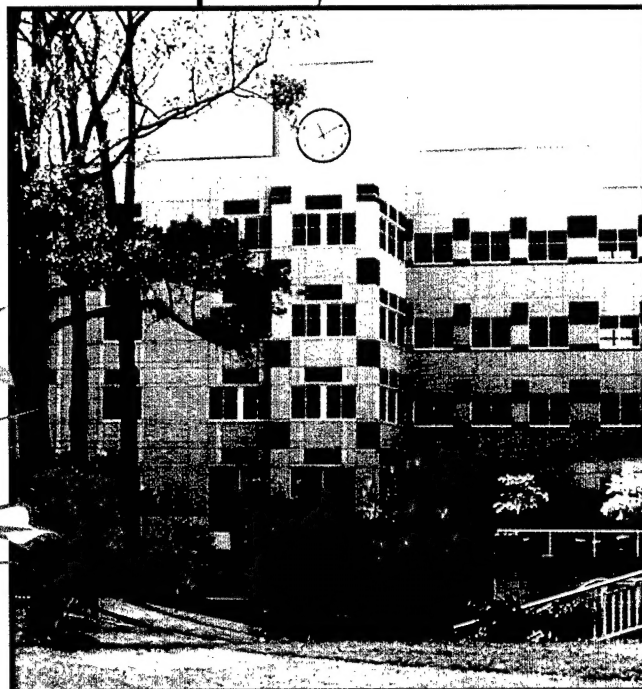
"Thank you for being so caring and compassionate."

"Thank you very much for the incredible support and reassurance that you gave me last month. Once again you put me at ease and took away my 'crisis.'"

"We are truly grateful for the work you are doing to beat cancer. Your dedication and commitment to those at risk is to be commended."

"Thank you for the informative seminar last evening. It helped to answer many questions I had, for which I could not find a satisfactory answer."

"You are a talented, efficient and humane (genuinely caring) staff. Thank you for your much needed service."

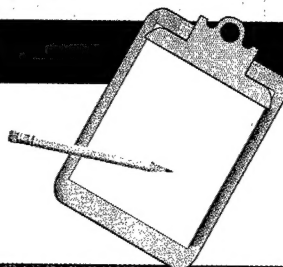


*Prevention Pavilion
at Fox Chase
Cancer Center*



THE MARGARET DYSON
Family Risk Assessment Program®




New Ovarian Cancer Screening Study




Fox Chase Cancer Center is participating in a new national ovarian cancer screening study. Currently women who are at an increased risk for ovarian cancer due to their family history or presence of a gene mutation are advised to have the CA125 blood test, pelvic exam and transvaginal ultrasound. These recommendations are made because they are the best screening tools we have to offer, even though they have limitations in detecting the disease at an early stage. The purpose of this new study is to learn whether measuring the CA125 more frequently than once a year is helpful in the early detection of ovarian cancer. This is a "pilot study" which will provide information to help plan a larger, more conclusive screening study in the future.


Who is eligible?

Healthy women who are considered at increased risk for ovarian cancer will be identified through FRAP. Women with or without ovaries may be eligible provided they are aged 30 and above, have not had ovarian cancer, and have met the following guidelines:

-  tested positive for the *BRCA1* or *BRCA2* genetic marker or have a close relative who has tested positive;
- OR
-  family history of two or more blood relatives with breast or ovarian cancers;
- OR
-  Ashkenazi Jewish ethnicity with a family history of one or more blood relatives with breast or ovarian cancer.

What does the study involve?

 Participants will come to Fox Chase Cancer Center every three months to have the CA125 blood test. A baseline questionnaire, collecting information about personal and family history, will be completed at the first visit, and a shorter follow-up questionnaire will be completed at the other visits. It is not necessary to see the doctor every time blood is drawn.

 Depending on the outcome of the blood tests, participants may be referred for a transvaginal ultrasound or a consultation with a gynecological oncologist.

Participants will be in the study for at least one year and up to two years. There is no cost for the CA125 blood tests or for any transvaginal ultrasounds that are recommended because of test results. FRAP clinic visits and yearly diagnostic studies, such as routine ultrasounds and mammograms, are not covered.

The search for better methods of detecting ovarian cancer is part of the mission at Fox Chase Cancer Center, and we hope this study will provide valuable information to help meet the goal. For more information, call 1-800-325-4145, and ask for information about the Ovarian Cancer Screening Study.

Hereditary Colon Cancer Study

Researchers at Fox Chase Cancer Center have recently received funding from the National Cancer Institute to study a gene mutation associated with an increased risk of colon cancer among the Ashkenazi Jewish population. This research project aims to learn about the significance of the mutation and to develop strategies for prevention of colon cancer in those who carry the gene mutation.

If you or a relative have had colon cancer and are Jewish and would be interested in participating in this study, please call 800-977-5232.

All genetic counseling sessions and genetic testing associated with the study are **free of charge and strictly confidential**.

UPDATE

Have you previously undergone predisposition genetic testing or are you interested in genetic testing? Your insurance company may now cover the cost of additional genetic testing or new genetic testing. If you are interested in learning more about what opportunities might be available to you through your insurance company, we invite you to call for more information.

Please call Anne Naumer at
215-728-7043 or 1-800-325-4145

Research Opportunities

Nutrition analysis (per serving):
Calories: 209; carbohydrate:
33 g; protein: 5 g; fat: 7 g;
fiber: 1 g; sodium: 400 mg

Source: Wheat Foods Council

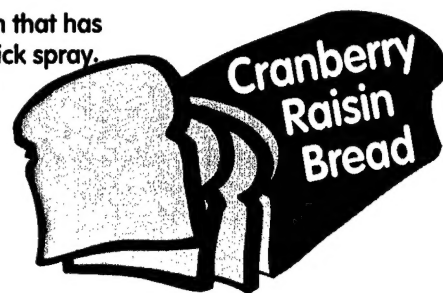


2-2/3 cups all-purpose flour
1 Tbsp. baking powder
1 tsp. baking soda
1 tsp. salt
1/4 tsp. pumpkin pie spice
1/2 cup margarine
1/2 cup brown sugar
1/2 cup orange marmalade
3/4 cup reduced-fat
cottage cheese, small curd
2 eggs, slightly beaten
grated rind of 1 lemon
grated rind of 1 orange
1/4 cup orange juice
1/2 cup golden raisins
1 cup cranberries,
coarsely chopped

Stir together flour,
baking powder, baking soda,
salt and pumpkin pie spice; set aside.

In a medium-sized bowl, cream together
margarine and brown sugar. Add marmalade,
cottage cheese, eggs, lemon rind, orange rind
and orange juice; mix thoroughly. Add flour
mixture and stir until just moistened. Fold in
raisins and cranberries.

Pour into a 9"x5"x3" pan that has
been coated with non-stick spray.
Bake at 325 degrees for
1 hour and 15 minutes.
Cool in pan 10 minutes;
remove from pan and
cool on a rack.
Makes 16 slices.



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Contributors: Carol Cherry, RNC, BSN, OCN

Graphic Design: Veronica Levin

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